PATENT COOPERATION TREATY

REC'D 30 MAR 2005
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PU4964WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/39619	International filing date *(day/month/year)* 12.12.2003	Priority date *(day/month/year)* 13.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D413/00		
Applicant SMITHKLINE BEECHAM CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.06.2004	29.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Stroeter, T Telephone No. +49 89 2399-8088

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/39619

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-101 as originally filed

Claims, Numbers

1-38 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-21 (in part), 22-27 and 36-38

   because:

   ☒ the said international application, or the said claims Nos. 22-27, 36-38 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-21 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-38
Industrial applicability (IA)	Yes:	Claims	1-21, 28-35
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 22-27 and 36-38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Subject-matter of the independent claims

The present application is directed to inhibitors of the chemokine-type CCR5 receptor which are useful in the treatment of viral diseases like HIV infections (independent claims 1 and 27) and the use thereof in the preparation of medicaments (independent claims 28 and 30). Furthermore pharmaceutical compositions comprising such compounds (independent claim 33) and methods of treatment (independent claims 22, 24, 26 and 36) are claimed.

2 Prior art documents

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: FINKE P E ET AL: "Antagonists of the human CCR5 receptor as anti-HIV-1 agents. Part 2: structure-activity relationships for substituted 2-aryl-1-[N-(methyl)-N-(phenylsulfonyl)ami no]-4-(piperidin-1-yl)butanes" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 2, January 2001 (2001-01), pages 265-270, XP004314863 ISSN: 0960-894X

D2: FINKE PAUL E ET AL: "Antagonists of the human CCR5 receptor as anti-HIV-1 agents. Part 3: a proposed pharmacophore model for 1-(N-(methyl)-N-(phenylsulfonyl)amin o)-2-(phenyl)-4-(4-(substituted)piperidin- 1-yl)butanes" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 18, 2001, pages 2469-2473, XP002962948 ISSN: 0960-894X

D3: DORN C P ET AL: "Antagonists of the human CCR5 receptor as anti-HIV-1 agents. Part 1: Discovery and initial structure-activity relationships for 1-amino-2-phenyl-4-(piperidin-1-yl)butanes " BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 2, January 2001 (2001-01), pages 259-264, XP004314862 ISSN: 0960-894X

Furthermore, the International Search Report mentions P-documents D4 and D5 which do not form part of the state of the art according to Rule 64.1(b) PCT:

D4: MAEDA K ET AL: "The current status of, and challenges in, the development of CCR5 inhibitors as therapeutics for HIV-1 infection" CURRENT OPINION IN PHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS,, NL, vol. 4, no. 5, October 2004 (2004-10), pages 447-452, XP004558853 ISSN: 1471-4892

D5: KUMAR S ET AL: "PHARMACOKINETICS AND INTERACTIONS OF A NOVEL ANTAGONIST OF CHEMOKINE RECEPTOR 5 (CCR5) WITH RITONAVIR IN RATS AND MONKEYS: ROLE OF CYP3A AND P-GLYCOPROTEIN" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 304, no. 3, 1 March 2003 (2003-03-01), pages 1161-1171, XP009019167 ISSN: 0022-3565

For the purposes of this communication the priorities of the present application and the above prior art have not been checked and it has been assumed that they are valid.

3 Novelty (Article 33(2) PCT)

The presently claimed compounds differ from the closest CCR5 inhibiting prior art

compounds of D1 and D2 through the cyclopropane ring, i.e. through the CH_2 group "bridging" the single C2-C3 bond in said prior art compounds. Thus, compound claims 1-21 and consequently further claims 22-38 appear to be novel.

4 Inventive step (Article 33(3) PCT)

The present application is directed to the problem of providing alternative CCR5 inhibitors for the treatment of viral diseases. The Applicant fails to cite specific test data to make credible that the claimed compounds actually solve the problem posed. However, even if such data is provided it is to be noted that the modification made starting from the structurally closest prior art compounds of D1, D2 (replacement of two H's with CH_2 to arrive at the cyclopropane moiety) appears to be a small structural variation and the skilled man would have expected that the present compounds have at least qualitatively the same pharmacological activity. Therefore said structural modification does not involve an inventive step.

If the Applicant, however, could convincingly argue that the modification made is not obvious then it is noted that there are more structural differences between tested examples given in the present description and compounds claimed in claims 1-21 then there are structural differences between the present example compounds and those of the closest prior art. Thus, in view of the tested examples which cover and as such provide support only for a restricted group of compounds, it is not obvious and therefore not credible that all embodiments embraced by the scope of the present claims do exhibit the stated pharmacological effect and as such solve the problem posed.

Furthermore, in view of D1-D3 it appears that the presence of certain structural features is fundamental for retention of the pharmacological activity, e.g. the substituent R^{10} is phenyl in all of the present examples and thus the present definition of R^{10} in claim 1 does not appear to be appropriate. The same must be stated for ring A which is either a piperidine or an 8-azabicyclooctane and for R^1-$(CH_2)_d$- which is also limited to NMe-SO_2-Ph as recommended in D1-D3 or NMe-CO-ring.

Thus, at present the subject-matter of the present set of claims is not inventive.

5 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present claims 1-21 and 28-35 is in accordance with the requirements of Article 33(4) PCT.

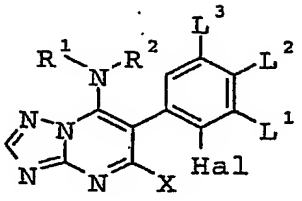
For the assessment of the present claims 22-27 and 36-38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6 Certain defects in the international application

The requirements of Rule 5.1(a)(ii) PCT are not met since the relevant background art has not been identified in the description.

Claims for invention 1:

1. Substituted 6-(2-halogenphenyl)-triazolopyrimidines of formula I



I

in which

Hal is halogen;

L^1, L^3 independently denote hydrogen, halogen, or C_1-C_4-alkyl;

L^2 is hydrogen, halogen, C_1-C_4-haloalkyl, or NH_2, NHR^b, or $N(R^b)_2$,

R^b is C_1-C_8-alkyl, C_3-C_{10}-alkenyl, C_3-C_{10}-alkynyl, C_1-C_6-haloalkyl, C_3-C_6-haloalkenyl, C_3-C_6-haloalkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_1-C_8-alkyl, C_3-C_{10}-cycloalkyl, or C(=O)-A, in which

A is hydrogen, hydroxy, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_6-halogenalkoxy, C_1-C_8-alkylamino or di-(C_1-C_8-alkyl)amino;

wherein at least one from L^1, L^2, and L^3 is not hydrogen;

X is halogen, cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy or C_3-C_8-alkenyloxy.

R^1 denote C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, or C_4-C_{10}-alkadienyl, C_2-C_{10}-haloalkenyl

wherein R^1 may be unsubstituted or may carry one to three groups R^a,

R^a is cyano, nitro, hydroxyl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_2-C_6-alkenyl, C_2-C_6-alkenyloxy, C_2-C_6-alkynyl, C_3-C_6-alkynyloxy, or C_1-C_4-alkylenedioxy;

R^2 is hydrogen;

2. Compounds of formula I according to claim 1, in which

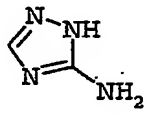
R^1 is straight chained or branched C_2-C_6-alkenyl, C_1-C_6-alkyl.

3. Compounds of formula I according to claim 1 or 2 in which X is halogen.

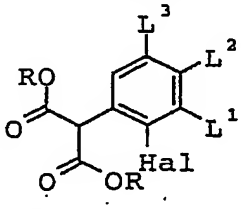
4. Compounds of formula I according to any one of claims 1 to 3 in which the 6-(2-halogenphenyl)group represents one of the following moieties:

2,3,5-trifluorophenyl, 2-F,4-CF_3-phenyl, 2-F,5-CH_3-phenyl, 2-Cl,4-F-phenyl, 2-F,4-Cl-phenyl, 2-F,4-Br-phenyl, 2-Cl,4-Br-phenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 2-F,4-NHC(O)CH_3-phenyl, 2-Br,3,5-difluorophenyl, 2-F,4-NO_2-phenyl, and 2-Cl,4-NO_2-phenyl.

5. A process for the preparation of compounds of formula I as defined in claims 3 and 4 which comprises reacting 5-amino-1,2,4-triazole

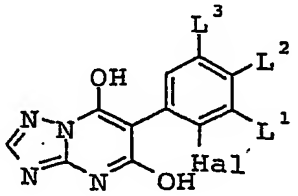


with 2-phenyl-substituted malonic acid ester of formula II,



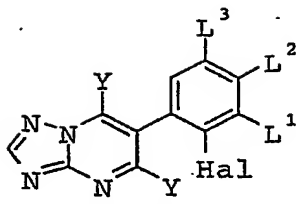
II

wherein Hal, L^1, L^2, and L^3 are as defined in formula I, and R denotes C_1-C_6-alkyl, under alkaline conditions, to yield compounds of formula III,



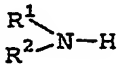
III

which are subsequently treated with a halogenating agent to give 5,7-dihalogen-6-phenyl-triazolopyrimidines of formula IV



IV

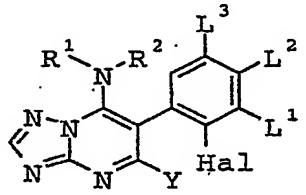
in which Y is halogen, and which is reacted with an amine of formula V



V

in which R^1 and R^2 are as defined in claim 1 to produce compounds of formula I, as defined in claim 1.

6. A process for the preparation of compounds of formula I according to claim 1 wherein X is cyano, C_1-C_{10}-alkoxy, or C_1-C_6-haloalkoxy, which comprises reacting 5-halogen-triazolopyrimidine of formula I',



I'

wherein Y is halogen, with compounds of formula VI,

M-X' VI

which are, dependent from the value of X' to be introduced, an anorganic cyano salt, an alkoxylate, haloalkoxylate or an alkenyloxylate, resp., wherein M is ammonium-, tetraalkylammonium-, alkalimetal- or earth metal cation, to produce compounds of formula I.

7. Intermediates of formulae II, III, and IV as defined in claim 5, in which the 6-(2-halogenphenyl)group represents one of the following moieties:

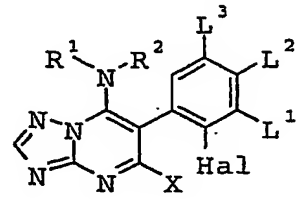
2,3,5-trifluorophenyl, 2-F,4-CF_3-phenyl, 2-F,5-CH_3-phenyl, 2-Cl,4-F-phenyl, 2-F,4-Cl-phenyl, 2-F,4-Br-phenyl, 2-Cl,4-Br-phenyl, 2,3-difluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 2-F,4-NHC(O)CH_3-phenyl, 2-Br,3,5-difluorophenyl, 2-F,4-NO_2-phenyl, and 2-Cl,4-NO_2-phenyl.

8. A composition suitable for controlling phytopathogenic fungi, comprising a solid or liquid carrier and a compound of the formula I as claimed in claim 1.

9. A method for controlling phytopathogenic fungi, which comprises treating the fungi or the materials, plants, the soil or the seed to be protected against fungal attack with an effective amount of a compound of the formula I as claimed in claim 1.

Claims for invention 6:

10. Substituted 6-(2-halogenphenyl)-triazolopyrimidines of formula I



I

in which

Hal is halogen;

L^1, L^3 independently denote hydrogen, halogen, or C_1-C_4-alkyl;

L^2 is hydrogen, halogen, C_1-C_4-haloalkyl, or NH_2, NHR^b, or $N(R^b)_2$,

R^b is C_1-C_8-alkyl, C_3-C_{10}-alkenyl, C_3-C_{10}-alkynyl, C_1-C_6-haloalkyl, C_3-C_6-haloalkenyl, C_3-C_6-haloalkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_1-C_8-alkyl, C_3-C_{10}-cycloalkyl, or C(=O)-A, in which

A is hydrogen, hydroxy, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_6-halogenalkoxy, C_1-C_8-alkylamino or di-(C_1-C_8-alkyl)amino;

wherein at least one from L^1, L^2, and L^3 is not hydrogen;

X is halogen, cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy or C_3-C_8-alkenyloxy.

R^1 and R^2 together with the interjacent nitrogen atom represent a saturated or partially unsaturated 5- or 6-membered heterocycle, containing one to four nitrogen atoms or one to three nitrogen atoms and one sulfur or oxygen atom, which ring may be substituted by one to three R^a radicals;

R^a is cyano, nitro, hydroxyl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_2-C_6-alkenyl, C_2-C_6-alkenyloxy, C_2-C_6-alkynyl, C_3-C_6-alkynyloxy, or C_1-C_4-alkylenedioxy;

11. Compounds of formula I according to claim 10, in which

R^1 and R^2 together with the interjacent nitrogen atom represent a heterocyclic ring with 5 or 6 carbon atoms being optionally substituted with one or two C_1-C_4-alkyl groups.

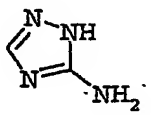
12. Compounds of formula I according to claim 10 or 11 in which R^1 and R^2 together with the interjacent nitrogen atom represent a 5- or 6-membered heterocyclic ring being optionally substituted with one or two methyl groups.

13. Compounds of formula I according to any one of claims 10 to 12 in which X is halogen.

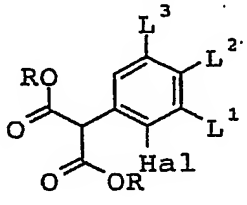
14. Compounds of formula I according to any one of claims 10 to 13 in which the 6-(2-halogenphenyl)group represents one of the following moieties:

2,3,5-trifluorophenyl, 2-F,4-CF_3-phenyl, 2-F,5-CH_3-phenyl, 2-Cl,4-F-phenyl, 2-F,4-Cl-phenyl, 2-F,4-Br-phenyl, 2-Cl,4-Br-phenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 2-F,4-NHC(O)CH_3-phenyl, 2-Br,3,5-difluorophenyl, 2-F,4-NO_2-phenyl, and 2-Cl,4-NO_2-phenyl.

15. A process for the preparation of compounds of formula I as defined in claims 13 and 14 which comprises reacting 5-amino-1,2,4-triazole

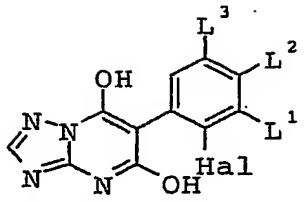


with 2-phenyl-substituted malonic acid ester of formula II,



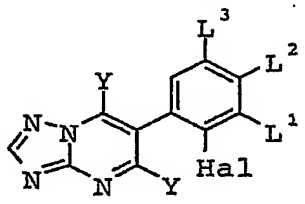
II

wherein Hal, L^1, L^2, and L^3 are as defined in formula I, and R denotes C_1-C_6-alkyl, under alkaline conditions, to yield compounds of formula III,



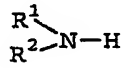
III

which are subsequently treated with a halogenating agent to give 5,7-dihalogen-6-phenyl-triazolopyrimidines of formula IV



IV

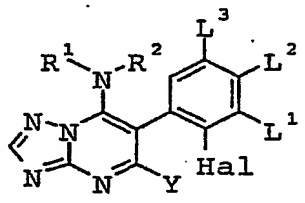
in which Y is halogen, and which is reacted with an amine of formula V



V

in which R^1 and R^2 are as defined in claim 10 to produce compounds of formula I, as defined in claim 10.

16. A process for the preparation of compounds of formula I according to claim 10 wherein X is cyano, C_1-C_{10}-alkoxy, or C_1-C_6-haloalkoxy, which comprises reacting 5-halogen-triazolopyrimidine of formula I',



I'

wherein Y is halogen, with compounds of formula VI,

M-X' VI

which are, dependent from the value of X' to be introduced, an anorganic cyano salt, an alkoxylate, haloalkoxylate or an alkenyloxylate, resp., wherein M is ammonium-, tetraalkylammonium-, alkalimetal- or earth metal cation, to produce compounds of formula I.

17. A composition suitable for controlling phytopathogenic fungi, comprising a solid or liquid carrier and a compound of the formula I as claimed in claim 10.

18. A method for controlling phytopathogenic fungi, which comprises treating the fungi or the materials, plants, the soil or the seed to be protected against fungal attack with an effective amount of a compound of the formula I as claimed in claim 10.